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EXPERIMENTAL STREPTOCOCCAL ARTHRITIS IN RABBITS.*

A SECOND STUDY DEALING WITH STREPTOCOCCI FROM THE MILK EPIDEMIC OF SORE THROAT IN CHICAGO, 1911-12.†

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In the article by Fritz Meyer[1] the literature of experimental arthritis is so thoroughly reviewed up to 1901 that only brief mention of the early investigations need be made. They chiefly concern clinical and bacteriological studies. The descriptions of the gross alterations are rather incomplete. Some exception to this is found in the accounts by Bannatyne, Wohlmann and Blaxall[2] of the changes produced in the joint by intravenous inoculation of an organism isolated from the inflammatory exudate in the joints of patients with rheumatism, an organism which they regarded as a bacillus. The description of the changes produced in rabbits' joints is as follows:

> "In the joints we found proof that the microorganisms grow and propagate, doing so not only in the synovial membrane, ligaments, etc., but also in the bone marrow and cartilaginous structures. Their presence gives rise to acute inflammatory changes leading to ulceration, erosion and destruction of the hard as well as the soft joint tissues. Our specimens are so few that this is only a provisional statement."

Meyer[3] produced an arthritis in rabbits with organisms isolated from rheumatic angina in 12 patients. The pathological anatomy is not described. Beaton and Ainley Walker[4] obtained joint affections in rabbits by the injection of micrococci isolated from cases of rheumatism, and of chorea and endocarditis in rheumatic subjects. Concerning this micrococcus they say: "culturally this organism resembles a streptococcus." Shaw[5] using organisms from three different sources, *Streptococcus aus chorea* obtained

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† See "Experimental Rheumatic Myocarditis," *Jour. Infect. Dis.*, 1912, 11, p. 243.

[1] *Verhandl. d. cong. f. inn. Med.*, 1901, 19, p. 452.

[2] *Lancet*, 1896, 1, p. 1120.

[3] *Op. cit.*

[4] *Brit. Med. Jour.*, 1903, 1, p. 237.

[5] *Jour. Path. and Bacteriol.*, 1903, 9, p. 159.

from Wassermann, Ainley Walker's *Micrococcus rheumaticus* and Poynton's *Diplococcus rheumaticus* produced practically all the lesions clinically associated with an attack of rheumatism. Similarly Beattie[1] speaks of intravenous inoculation of *Diplococcus rheumaticus* recovered from congested areas about the knee joint in a case of rheumatic fever. Cole[2] described the changes produced in rabbits by the injection of seven different strains of streptococci from sources other than acute rheumatism without, however, attempting to follow the changes as they develope from early to late. Harris[3] produced arthritis in rabbits following the injection into the circulation of streptococci isolated from human sepsis and pharyngitis. Koch[4] produced a condition resembling articular rheumatism in young dogs by intravenous injection of *Streptococcus longus*. He emphasizes the predilection epiphyseal cartilages and the regions about them possess for initial changes.

In a number of articles by Poynton and Paine there are references to the changes in the joints. In an early publication[5] they state:

> "There was also exudation into the tendon sheaths around the affected joints and the connective tissue near the larger joints had the gelatinous appearance of the nodule in man. We demonstrated the diplococci in the valves, pericardium, joint exudate, liver, kidneys, connective tissues around the joints and in large numbers in the lungs and pleurae." In the same article, referring to the bacteria in the tissues about the blood vessels in the pericardium and myocardium, they say: "In the earliest stages these organisms can be discovered in these tissues without having apparently caused any reaction, but a proliferation of connective tissue cells and a free exudation of leukocytes is usually easily recognized as a result of their presence." In another publication[6] there is the following description of the changes in the joint of a rabbit killed 10 weeks after inoculation. "The right knee was enlarged and the articular surfaces distinctly though slightly flattened. The edges of the articular surfaces were rounded, and if compared with the corresponding joint, thickened, giving rise to some lipping. A thickening on the inner condyle of the femur was especially noteworthy. In two places on the outer condyle of the femur the bone was eroded and the cartilage destroyed. There was both bone formation and bone destruction. The cartilage on the tibia had lost its natural gloss, and with a lens was seen to be roughened and pitted. . . . . The atrophy of the muscles around the joint was very evident. The joint

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[1] *Jour. Path. and Bacteriol.* 1904, 9, p. 272.

[2] *Jour. Infec. Dis.*, 1904, 1, p. 714.

[3] *Trans. Chicago Path. Soc.*, 1905, 4, p. 303.

[4] *Ztschr. f. Hyg. u. Infectionskrankh.*, 1912, 72, p. 321.

[5] *Lancet*, 1900, 2, p. 861.

[6] *Trans. Path. Soc.*, London, 1902, p. 221.

capsule was not greatly thickened, but the ligaments, especially the crucial, were opaque and swollen. . . . . Whatever the causes of rheumatoid arthritis may be this appears to be quite certain, that if it is the result of an infection, the paths of access are far distant from the joints, and these structures are damaged because they are particularly susceptible, and not because there is direct invasion by microorganisms as in traumatic arthritis, the result of a wound." In a later article[1] they say: "The organism is deposited in the areolar tissue below the free margin of the synovial membrane," and that it "multiplies and flourishes in the local lesion and the blood stream is only a channel of conduction." Considering the origin of the inflammatory process in the joints, Poynton[2] remarks: "There is as can be imagined considerable difficulty in discovering with exactitude in which structure the process commences, but as far as the infective forms are concerned the balance of evidence points to the synovial membrane as the starting point in the majority of instances. The vascular supply is very considerable and the synovial membrane in a condition of acute inflammation." Of the infective agent, he says: "It is carried into the terminal capillaries by the blood stream and escaping finds itself in the retiform tissue of the membrane." He further observes: "The condition of the blood vessels in the capsule and synovial membrane is also of interest. In these protracted cases there is a perivascular exudation and later a perivascular fibrosis which interferes with the circulation in these structures and thus impairs the recuperative power."

There is still more of detail in the recent article by Coombs, Miller and Kettle.[3] The alterations in the joints of a rabbit, killed six days after intravenous inoculation with streptococci isolated from the vegetations on the tricuspid valve in a case of rheumatism, are thus described:

> "The synovial membrane shows the formation of many fibroblasts, also new capillaries. The vascular endothelia are proliferating in some instances so much as to obliterate the vessel. In places there are groups of cells with much cytoplasm and one or more clear, transparent nuclei. Several vessels are completely occluded by thrombosis, others by masses of homogeneous material mixed with organisms. The whole of the synovial membrane and periarticular tissue are infiltrated with eosinophil leukocytes, which are also poured out freely into the cavity of the joint. A few of these are degenerating, but for the most part they have kept their structure well."

Concerning changes similar but somewhat more advanced in the joints of a rabbit which received two intravenous injections, the first producing arthritis from which the animal recovered, the second given four months and nine days later resulting in arthritis and death 16 days after the last inoculation, they say:

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[1] *Lancet*, 1905, 2, p. 1760.

[2] *Med. Press and Circular*, 1907, p. 360.

[3] *Lancet*, 1912, 2, p. 1209. These authors duplicate my observations on the experimental production of myocardial lesions in rabbits, similar to those found in human "rheumatic myocarditis," by intravenous injection of streptococci.

"Throughout the synovial membrane there is a diffuse fibroblastic reaction, very intense but without leukocytosis. Practically all the small vessels and most of the large ones display a definite endothelial proliferation. There are also fibroblastic rings about them. The endovascular reaction has in one or two places ended in thrombosis; but as a rule it reaches its highest expression in the formation of typical 'submiliary nodules.'" With regard to the condition in another joint they state: "In the joint the similarities and differences between clinical and experimental rheumatism are exemplified. The reaction in the synovial tissues was mainly gathered together into rounded masses curiously like the subcutaneous nodes seen in rheumatic children. Some of these consist entirely of (*a*) many blood vessels most of them with swollen and proliferating endothelium, sometimes so far developed as to constitute a 'submiliary nodule' in embryo; (*b*) fibroblasts lying in every plane, but especially arranged in whorls around blood vessels; (*c*) a diffuse but moderate leukocytosis. In others (and here it is that the characteristics of the experimental type of lesion are exemplified), there are large masses which seem to consist of streptococci lying in the center of the inflamed areas; round these masses the leukocytosis was more intense and there were definitely necrotic changes."

Joint affections were frequent in the milkborne epidemic[1] of sore throat in Chicago during 1911 and 1912. Reference to the frequency of arthritis as a sequence of such streptococcus infections of the throat is made by a number of writers[2] not only concerning the Chicago epidemic but also in others. The occurrence of inflammation in the joints of rabbits inoculated with organisms isolated by Dr. Davis in the course of the Chicago epidemic has been mentioned in previous articles.[3] The material accruing from the experiments was nearly all fixed in Zenker's fluid and after decalcification the sections were stained by various standard methods, hematoxylin and eosin, phosphotungstic acid hematoxylin, polychrome methylene blue and eosin, the Giemsa and Wright methods for bacteria, etc.

Changes in two rabbits killed two and four hours respectively after single injections of the 24-hour growth at 37° C. on two blood agar slants of a streptococcus (236) from the serofibrinous peritoneal exudate found at necropsy, and producing arthritis in rabbits. The peritonitis was a sequence of sore throat during the milk epidemic.—In sections of the joints of these two rabbits, streptococci are found in some of the capillaries of the synovial membrane. The organisms are not in sufficient numbers to occlude the vessels but are scattered rather evenly among the blood cells. Aside from this there are no changes in the tissues.

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[1] J. A. Capps and J. L. Miller, *Jour. Am. Med. Assn.*, 1912, 58, p. 1912.

[2] Robinson, *Practitioner*, 1884, 32, p. 467; Hall, *Glasgow Med. Jour.*, 1890, 34, p. 241; Sömme, *Lancet*, 1908, 1, p. 1707; Winslow, *Jour. Infect. Dis.*, 1912, 10, p. 73; Davis, *Illinois Med. Jour.*, 1912, 22, p. 585; Hamburger, *Bull. Johns Hopkins Hosp.*, 1913, 24, p. 1, (one case).

[3] *Jour. Am. Med. Assn.*, 1912, 58, p. 1283; *Jour. Infect. Dis.*, 1912, 11, p. 243.

Changes in a rabbit killed 10 hours after a single intravenous injection of the same streptococcus (236), using the growth from four blood agar slants after 24 hours at 37° C.—Microscopic preparations of the carpal and tarsal joints were examined. In places the capillaries of the synovial membrane contain streptococci which are also present in small numbers in the joint cavity. In the latter location they occur in pairs or short chains of four or six organisms surrounded by a small amount of a pink-staining material without cells. This material does not give the staining reaction of fibrin. In sections of the carpal joint a few vessels in the diaphysis of the radius near the epiphyseal cartilage are crowded with polymorphonuclear leukocytes and in the same region and just at the edge of the cartilage is a small vessel filled with cocci. There is no necrosis of the tissues. Also in sections of the carpal joint, many of the vessels in a triangular portion of the tibia with one side at the outer anterior surface of the bone and another along the epiphyseal cartilage, contain bacteria which completely occlude the vessels beneath the periosteum.

Changes in a rabbit killed 24 hours after a single injection of the growth on two blood agar slants of the same streptococcus (236).—Sections from both carpal joints were examined. The cavities of one joint are not involved; those of the other contain a moderate amount of exudate (Fig. 1) in which there are many organisms. The cells present in this exudate are chiefly polymorphonuclear leukocytes. There are a few places in the synovial membrane where the inner layer of cells is necrotic but in general this layer of cells appears fairly well preserved. The blood vessels contain a moderately increased number of polymorphonuclear leukocytes. In a few places small vessels are found containing bacteria and about them there is an infiltration of polymorphonuclear leukocytes and mononuclear cells. There is necrosis of the fibro-cartilaginous zone in some places. The changes being so alike in both joints, one description will answer for both. There is little or no involvement of the carpal bones, but the epiphyseal cartilage, the cancellous bone and the bone marrow on either side of the cartilage and the periosteum in this region of the long bones, are the seat of many lesions. There is a triangular region in the diaphysis of one of these bones having one side at the epiphyseal cartilage and including about one-fourth of the diameter of the cartilage, and another side at the outer surface of the bone and extending for a distance of about 1.5–2 mm. in which necrosis is marked and bacteria numerous. There is also a smaller necrotic region about the middle of the epiphyseal cartilage and including the bone on either side for a short distance. There is no inflammatory reaction about either of these regions. Organisms are present in practically all parts of the cancellous bone of the diaphysis and for a considerable distance from the epiphyseal cartilage in the epiphysis, also in many of the vessels of the compact bone. There are lesions of the bone marrow having an irregular arrangement of a deeply red-stained substance, bacteria and cells in which there is much nuclear fragmentation. In one such small lesion there is running through it a deep red-stained portion having the outline of a vessel and on either side of it are deeply stained cells, polymorphonuclear leukocytes and mononuclear cells. Bacteria are present both in the red-stained portion and among the cells surrounding it. At certain points in the marrow, usually next to the bone, there are rather large spaces, 0.5 mm. in length by about one-third that width, filled with bacteria alone and surrounded with marrow and bone that stain well. The lesions in the periosteum extend for a distance of 1–2 mm. along the diaphysis and for a much shorter distance along the epiphysis. Sometimes a single lesion extends along the periosteum for a distance of 1–2 mm. At other times there are a number of small lesions separated by short intervals. They are of the same general character as those described in the bone marrow.

Changes in a rabbit dying two days after a single intravenous injection of the 24-hour growth on one blood agar slant of a streptococcus (211) isolated from a case of "streptococcus septicemia" in the Chicago milk epidemic of 1912.—Sections of the two carpal joints were examined. Streptococci are present in the blood vessels in all parts of the sections. There is a moderate amount of exudate in the joint cavities and in it are bacteria and a few cells. The synovial membrane and articular cartilages do not appear to be injured. There is extensive necrosis of the bone and bone marrow in the long bones, especially in the diaphyses, and to a less extent in the epiphyses and carpal bones. There is complete necrosis of portions of the diaphysis bordering on the epiphyseal cartilage, and a large number of organisms are present in these locations. Also in places, large masses of organisms separate the periosteum from the underlying bone. Where the bone marrow is not so greatly altered the vessels are filled with cocci. There is no reaction in any of the tissues.

Changes in a rabbit dying two days after a single intravenous injection of the 24-hour growth on one blood agar slant of a streptococcus (213) from peritoneal fluid in a case of peritonitis secondary to sore throat.—The changes found in the joints of this rabbit are quite similar to those found in the joints of the preceding rabbit.

Changes in a rabbit dying two days after a single injection of the 24-hour growth from one blood agar slant of a streptococcus (214) from suppurating lymph glands secondary to sore throat.—Sections from one carpal joint and one metacarpophalangeal joint were examined. The joint cavity of the metacarpophalangeal joint is not involved, but the cavities of the carpal joint contain a rather large amount of exudate in which are a large number of bacteria. Cells are not very numerous and consist of polymorphonuclear leukocytes and mononuclear cells which stain fairly well. The inner layer of cells of the synovial membrane is quite well preserved except in the recesses of the cavities where it is often necrotic. The blood vessels of the synovial membrane are distended with blood. There are many small collections of bacteria, some occupying the lumen of vessels with no inflammatory reaction about them. There are a few small necrotic regions containing scattered chains of cocci and surrounded by cells in which there is much nuclear fragmentation. There is also a considerable number of large mononuclear cells in the connective tissue of the plica synovialis especially near the blood vessels. There are a few necrotic places in the articular cartilages, one extending nearly the entire depth of the cartilage, otherwise there are no changes. In sections of the first phalanx of one of the toes, 0.5 mm. below the epiphyseal cartilage, there is a lesion in the bone marrow about 0.75 mm. square and occupying about one-fourth the diameter of the bone at this point. On three sides there is a zone of infiltration varying from one-tenth to one-sixth the diameter of the lesion, quite sharply demarcating it from the marrow. The fourth side, that nearest the epiphyseal cartilage, borders on necrotic cancellous bone and here, there is only a slight infiltration of cells. The infiltrating cells are mononuclear and polymorphonuclear leukocytes with a considerable number of eosinophils. The center of this lesion is occupied by cocci, arranged in long chains quite evenly distributed and not crowded. Neither necrotic material nor cells are present. The cancellous bone and the bone marrow near the epiphyseal cartilage are almost completely necrotic and the compact bone on one side is extensively involved for a distance of 2.5 mm. from the epiphyseal cartilage. The blood vessels contain numerous bacteria and the bone surrounding them is necrotic.

The periosteum covering this portion of the bone contains a lesion extending lengthwise of the bone for 2 mm. There is no reaction about any of the last mentioned lesions. A similar condition is present in the other long bones included in the sections. No lesions were observed in the bone marrow of the epiphysis or of the carpal bones.

Changes in a rabbit dying two days after a single intravenous injection of the 24-hour growth on one blood agar slant of a hemolytic streptococcus (200) from the crypts of normal tonsils.—Sections of the right carpal and left tarsal joints were examined. The cavities of both are filled with a very abundant exudate consisting of a granular, lightly hematoxylin stained material, cellular debris and organisms. The articular cartilages are very largely necrotic and in places there are erosions which extend entirely through them and communicate with abscesses in the bone marrow. The synovial membrane is also necrotic and the necrosis also extends for a considerable distance into the adipose tissue of the plica synovialis and the connective tissue immediately about the cavities. Separating the necrotic portions from the more normal tissues in certain places is a zone of cellular infiltration in which karyolysis is marked. Where the sections have been made across the prolongation of the synovial membrane laterally, the appearances obtained are those of an abscess. The tissues surrounding the joint cavities laterally are very edematous. There is a slight increase in the number of polymorphonuclear leukocytes and an increase in the mononuclear cells especially about blood vessels. In the tarsal joint the larger number of these cells are of the smaller more deeply staining type, occurring in groups of 20 to 50 cells or scattered more or less evenly through the tissue; in the carpal joint the large endothelial cells predominate. There are small regions of necrosis at various points in these tissues, often occurring in connection with blood vessels. Sometimes the entire vessel is included in the necrosis, sometimes there is a narrow band of necrosis surrounding a vessel or group of vessels. The endothelium is usually swollen and the vessel wall infiltrated with mononuclear cells and polymorphonuclear leukocytes. Lesions of the bone marrow are fairly numerous in the carpal bones especially near the articular cartilages. Most of them are small, well defined, necrotic regions in which there is infiltration of mononuclear cells and leukocytes. Bacteria are not always found. Others consist simply of collections of small, deeply stained, mononuclear cells. No lesions are found in the epiphyseal cartilages or the bone marrow near them. Some of the tendon sheaths contain an exudate similar to that found in the joint cavities, accompanied by necrosis of the tendon sheath, and an infiltration of the surrounding connective tissue with mononuclear cells and polymorphonuclear leukocytes.

Changes in a rabbit killed four days after a single injection of the 24-hour growth from one blood agar slant of a streptococcus (242) isolated from the maxillary sinus.—This rabbit was killed four days after injection. Sections from both carpal joints were examined. The joint cavities contain an abundant exudate consisting of a granular pink-stained material irregularly distributed, polymorphonuclear leukocytes, mononuclear cells and very large numbers of bacteria. The synovial membrane is quite generally necrotic near its attachment to the cartilages but in other places especially covering the plicae it is very well preserved. There are a few small patches of superficial necrosis in some of the articular cartilages. There are no lesions in the bone marrow of the carpal bones. In both radius and ulna of the same leg, there is in the diaphysis at one side, a triangular shaped piece of bone in which necrosis is complete. One side of the triangle lies along the epiphyseal cartilage and in the larger of these lesions extends about 2 mm. or nearly half the diameter of the bone. Another side lies along the edge of the bone and is about 4 mm. in length. The periosteum is included in this lesion. Bacteria are very numerous in the marrow spaces and periosteum. There is no reaction about the lesion. In sections through the other carpal joint there is in one of the long bones necrosis of the bone and bone marrow of the epiphysis bordering on the epiphyseal cartilage for about four-fifths of its diameter and extending about one-half of one millimeter in the direction of the joint. Lesions similar to those in the periosteum are found in some of the tendon sheaths. Necrosis is marked and bacteria are numerous.

Changes in a rabbit killed five days after a single intravenous injection of the 24-hour growth on two blood agar slants of a hemolytic streptococcus (192) isolated from the tonsils of a child five years old giving a history of tonsillitis associated with joint involvement eight months previous.—Microscopic preparations of both carpal joints were examined. The cavities of the right joint contain a finely granular, lightly hematoxylin stained material, which probably represents fluid before it was fixed, and in it are bacteria and cells, many of which are disintegrating. There is extensive, sometimes complete necrosis of the synovial membrane, and the plica synovialis, and also the connective tissue immediately adjoining them. The articular cartilages are largely necrotic, and erosions extend entirely through them to the bone marrow. There is edema of the tissues surrounding the joint laterally, and an infiltration of mononuclear cells and leukocytes which is especially conspicuous about the blood vessels. Scattered through these tissues are many necrotic regions of varying size about some of which there is a cellular infiltration with much nuclear fragmentation. Occasionally the lumen of a vessel is found filled with bacteria and cells, chiefly mononuclears accompanied by little necrosis. One of the carpal bones is almost entirely necrotic; in others there is little necrosis of the bone, but small abscesses are numerous in the bone marrow bordering on the articular cartilages. There is also an occasional abscess in the bone marrow of the epiphyses of the long bones next to the articular cartilages or in the bone marrow of the diaphyses. There is an involvement of the tendon sheaths about the joint, which is quite similar to that of the joint cavities.

The process is accompanied by much less necrosis in the left carpal joint. The joint exudate is less abundant and contains fewer bacteria and more leukocytes, and there is less disintegration of cells. The synovial membrane is necrotic in places, especially in the recesses of the cavities. The adjoining connective tissue for a short distance is usually included in the necrosis. There is a moderate increase in the number of polymorphonuclear leukocytes in the surrounding connective tissue, especially near the joint cavities and about some of the blood vessels. Most conspicuous, however, is the infiltration of mononuclear cells around blood vessels (Fig. 2) in the connective tissue about the joints and tendon sheaths. This infiltration or proliferation of cells is sometimes outside the vessel wall on one side or, entirely surrounding it at other times, it is within the vessel wall (Fig. 3) beneath the endothelium, which is pushed forward into the lumen partially closing the latter. Some of the collections consist entirely of the large endothelioid cells, others of a combination of these with the smaller mononuclear cells and leukocytes. The tendon sheaths are infiltrated with mononuclear cells and leukocytes. Destruction is not extensive. In one tendon sheath there are alternate layers of cells staining blue and a deeply red-stained material containing a few polymorphonuclear leukocytes, making in all five layers, three blue and two red. The cells are mostly large mononuclears and polymorphonuclear leukocytes. There are a few superficial erosions of the articular cartilages but

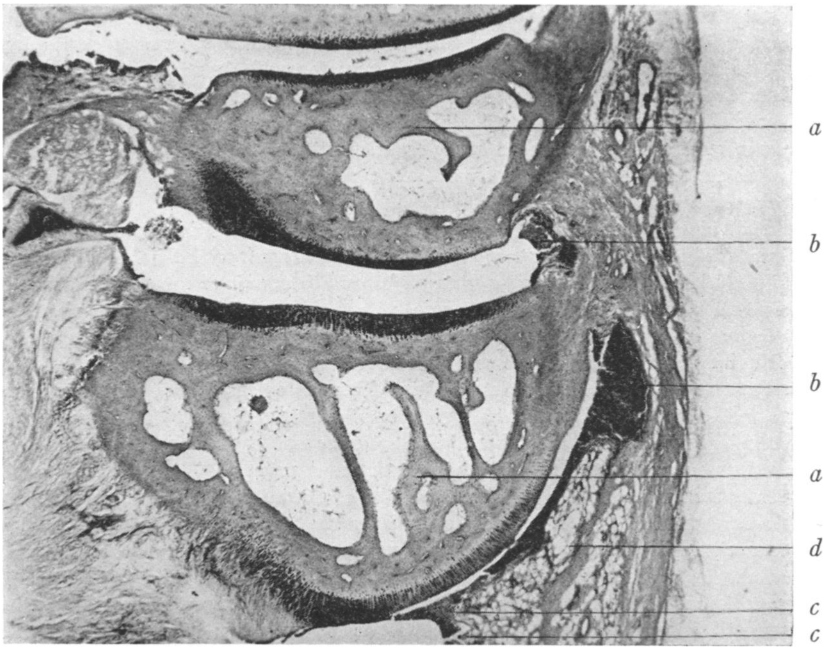

FIG. 1.—Exudate in the wrist joint cavities of a rabbit killed 24 hours after injection of streptococcus 236.

a. Carpal bones.
b. Exudate in joint recesses.
c. Synovial fringes.
d. Adipose tissue in the plica synovialis.

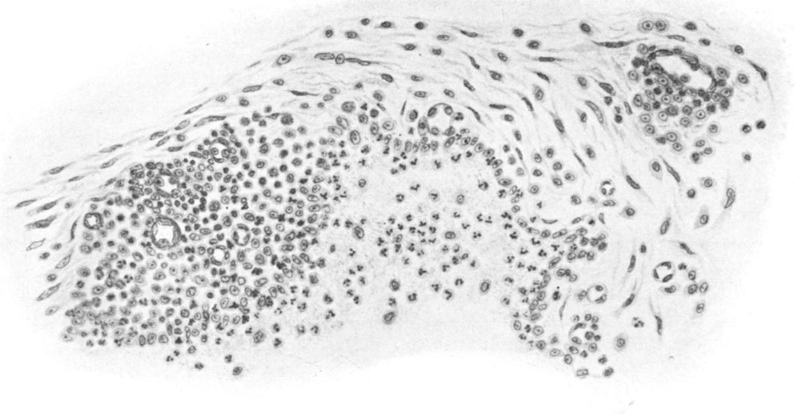

FIG. 2.—Small nodule adjacent to the synovial membrane, collection of mononuclear cells on one side of a small blood vessel and exudate in the joint cavity of a rabbit killed five days after injection of streptococcus 192.

no lesions of the epiphyseal cartilages, bone, or bone marrow were observed in this joint.

Changes in a rabbit dying seven days after a single injection of the 24-hour growth of a streptococcus (218) isolated from the sero-fibrinous exudate of pleurisy following sore throat.—The cavities of the ankle joint contain an exudate rich in cells which are largely polymorphonuclear leukocytes, and a few mononuclear cells with very little nuclear fragmentation or other evidence of necrosis, and many capsulated streptococci. The cells seem to be held together by a granular material which was formerly a fluid present in the joint cavity. In places this material is in the form of a very fine meshwork staining red in hematoxylin and eosin preparations, and resembling fibrin. The articular cartilages and synovial membrane appear to be very little injured except where the exudate is thickest next to the fringes that project into the cavity from in front. Here there is a diffuse infiltration with polymorphonuclear leukocytes and destruction of the surface covering of synovial membrane. The tendon sheaths contain bacteria and are infiltrated with leukocytes and mononuclear cells with very little necrosis. There is a triangular lesion (Fig. 4) in the anterior portion of the diaphysis of the tibia, the sides being 1.5, 1, and 1 mm. respectively. It is bounded on one side by the epiphyseal cartilage, on another by the periosteum and on the third by the bone and bone marrow of the shaft. The bone and bone marrow are completely necrotic, the spaces being filled with bacteria and there is no infiltration of cells except along the side next to the epiphyseal cartilage. Hemorrhages are present in the bone marrow of the shaft 1.5 cm. from the joint surface. These are 1–1.5 mm. in diameter and occupy about two-thirds of the diameter of the shaft at that point. Sections of two toe joints were examined (Fig. 5), and in addition to the changes found

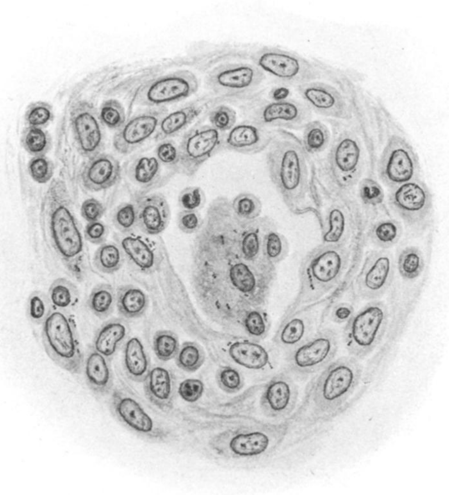

FIG. 3.—Collection of large and small mononuclear cells about a blood vessel containing a clot. Streptococci in the clot and in some of the cells. From a rabbit killed five days after injection of streptococcus 192.

in the ankle joint, there are several small lesions in the bone marrow about 1.5 cm. proximal to the epiphyseal cartilage and located along the edge of the compact bone. These lesions are well defined and the largest is about 0.5 mm. in its longest dimension. There is an infiltration of mononuclear cells in the outer portions of the lesions and in the center are bacteria and much nuclear fragmentation. There is an infarct in the diaphysis of a bone of one of the toes quite similar to that described in the tibia. The epiphyseal cartilage in one of the bones of the other toe is completely dissected away from the cancellous bone of the diaphysis by a cellular exudate.

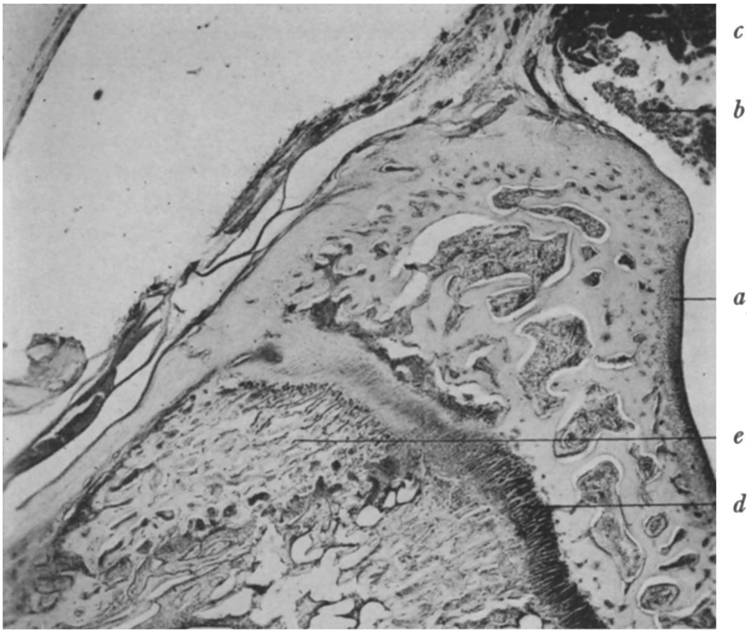

FIG. 4.—Infarct in the diaphysis of the tibia of a rabbit dying seven days after inoculation with streptococcus 218 from the sero-fibrinous exudate of pleurisy following sore throat.

a. Articular cartilage.
b. Exudate in joint cavity.
c. Synovial fringes.
d. Epiphyseal cartilage.
e. Infarct.

Changes in a rabbit dying 11 days after a single injection of the 24-hour growth on one blood agar slant of a streptococcus (217) isolated from suppurating lymph glands following sore throat.—Microscopic preparations of both carpal joints were examined. The cavities of these joints contain an abundant, finely granular, lightly hematoxylin stained exudate in which are a few cells, many bacteria, and scattered patches of eosin staining material. Fibrin was demonstrated in this exudate. The synovial membrane and plicae synovialis are completely destroyed and the necrosis extends more or less into the tissues about the recesses of the cavities and from these points lengthwise along the outer margin of the bones, in some cases as far as the epiphyseal cartilage. The tissues surrounding these necrotic regions are edematous and densely infiltrated with mononuclear cells chiefly of the smaller variety. The blood vessels also contain many more than the normal number of mononuclear cells. Polymorphonuclear leukocytes are not greatly increased in numbers. Small foci of necrosis occur in these tissues in various places, and within and also about them as also in the tissue immediately surrounding the larger necrotic regions before described, there is a large amount of nuclear

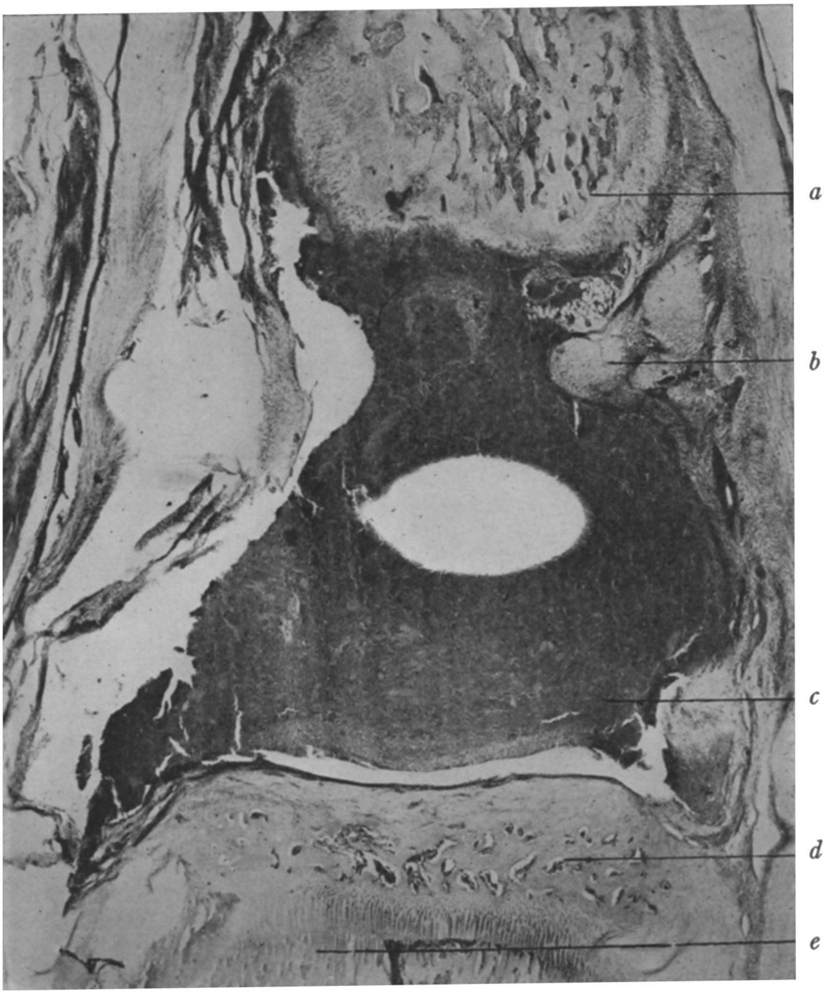

FIG. 5.—Large exudate in the metacarpo-phalangeal joint of rabbit dying seven days after inoculation of streptococcus 218 from the sero-fibrinous exudate of pleurisy following sore throat.

a. First phalanx of the toe.
b. Plica synovialis.
c. Large exudate in the joint cavity.
d. Metacarpal bone.
e. Infarct.

fragmentation. The cavities of the other joint contain a rather scanty exudate in which cells are quite numerous, some containing organisms but with little evidence of necrosis. There is very little injury of the synovial membrane except in a few places in the recesses of the cavities and some of the synovial fringes. There are a few regions of superficial necrosis in the articular cartilages. In the epiphysis of the radius just distal to the epiphyseal cartilage there is necrosis of the bone and bone marrow extending through nearly the entire diameter of the bone at that point and for about 0.5 mm. distalward. The epiphysis (Fig. 6) is practically dissected from the epiphyseal cartilage by a cellular exudate. In one place necrosis extends through the epiphyseal cartilage. There is some nuclear fragmentation of the cells of the bone marrow bordering on the lesion but the lesion is not sharply defined. There is also an infarct in the diaphysis of the radius resembling those described in bones of other joints.

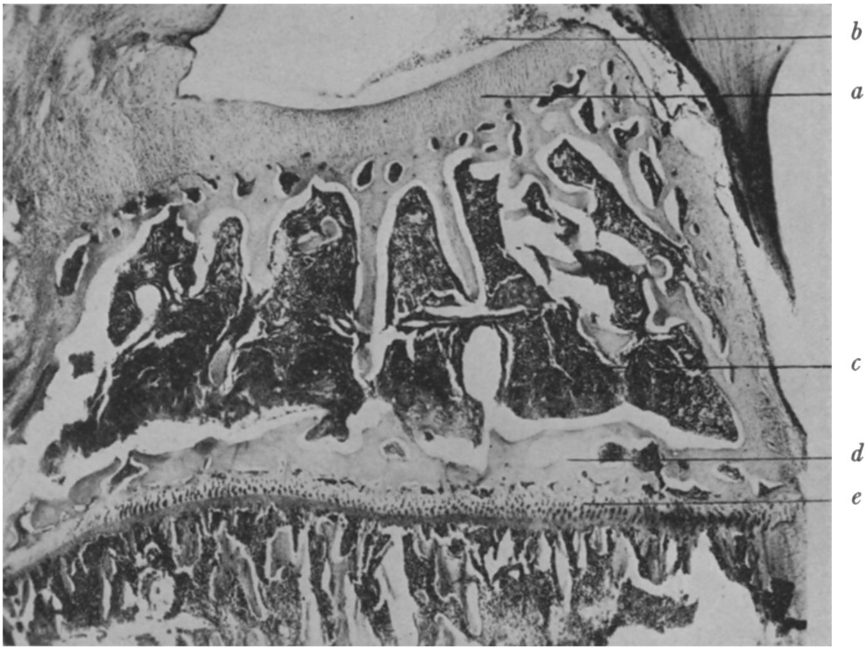

FIG. 6.—Partial necrosis of the epiphysis and epiphyseal cartilages of the radius of a rabbit dying 11 days after inoculation of streptococcus 217 from suppurating lymph glands secondary to sore throat.

a. Articular cartilage.
b. Exudate.
c. Cellular exudate in the marrow spaces of the epiphysis.
d. Necrotic bone.
e. Epiphyseal cartilage.

Changes in a rabbit killed 13 days after a single injection of a streptococcus (236) on a single blood agar slant.—Sections of the carpal, elbow, and knee joints were examined. The cavities of the carpal joint contain an abundant necrotic exudate and numerous bacteria. The synovial membrane is absent and the plicae synovialis are necrotic. In the connective tissue about the joint there is the usual mononuclear infiltration and scattered foci of necrosis. The articular cartilages are necrotic for the greater part of their depth and there are many small necrotic regions in the marrow of the carpal bones near the cartilages. The cavity and synovial membrane of the elbow joint appear normal. There are a few collections of mononuclear cells about small blood vessels in the connective tissues surrounding the joint cavity laterally. In the diaphysis of the ulna about 1.5 mm. from the proximal end of the bone, there is a small region of necrosis in the compact bone. The blood vessels in this portion of the bone are filled with a granular eosin stained material and many cocci. In the cancellous bone of the diaphysis next to the epiphyseal cartilage there is an infarct about 1.5 mm. in its longest dimension, that lies along the epiphyseal cartilage, and about 2 or 2.5 mm. proximal, and in the middle of the bone marrow there is a partially necrotic cell exudate. The cavity of the knee joint is distended with a necrotic exudate in which are large numbers of organisms. The synovial membrane is entirely absent and the connective tissue surrounding the cavity is necrotic for a variable distance from the margin. In one place the necrosis extends entirely through the tissues covering the joint anteriorly for a distance of 2 mm. There is a mononuclear infiltration of the connective tissue and muscle surrounding the joint cavity. The articular cartilages are necrotic for from one-half to two-thirds their depth, but no erosions are observed. No lesions of the bone or bone marrow are found. The tendon sheaths about the joint contain an exudate similar to that in the joint cavity and there is extensive necrosis of the surrounding connective tissues. The infiltrating cells are largely small mononuclears with comparatively few leukocytes and the infiltration is most marked about blood vessels.

Changes in a rabbit killed two months and nine days after intravenous inoculation of the growth on one blood agar slant of a hemolytic streptococcus (256) isolated from the tonsils of a man aged 42 years, suffering from typical chronic arthritis of about one year's duration. These attacks of febrile exacerbation occurring every four to six weeks were accompanied by swelling of the wrist, shoulder, ankle and knee joints. The heart and kidneys were normal. The tonsils were moderately enlarged and not accutely inflamed. A practically pure growth of hemolytic streptococcus was obtained from plate culures made from the crypts of both tonsils.—Sections of the shoulder joint, the only joint involved, were examined. The inflammatory process in this joint differs considerably from that found in earlier stages, in the relatively great number of cells corresponding to the large mononuclear leukocytes, cells called by some, "endothelial," and markedly phagocytic. The joint cavity contains a moderate amount of exudate consisting of necrotic material and numerous cells, many partially disintegrated. These are chiefly polymorphonuclear leukocytes with a few mononuclear cells, some of which are very large. The synovial membrane is absent, and about the margins of the cavity ordinarily covered by it, is a heavily infiltrated region 0.5–1 mm. in thickness and necrotic near the cavity. The infiltrating cells are for the most part mononuclear cells with polymorphonuclear leukocytes scattered throughout and a few multinucleated giant cells in places. The mononuclear cells, both the large and small variety, are about equally numerous, the large cells more abundant close to the cavity and the small cells more abundant distant from the cavity. The large cells vary greatly in size and shape, are lightly stained with pale, round or oval nuclei, which are usually eccentrically placed and possess a large amount of cytoplasm, which is often loaded with detritus, pigment or bacteria. The cells containing pigment occur in groups and are usually located at some distance from the cavity. The small cells referred to are lymphocytes and plasma cells. At the peripheries of this infiltrated region, they are aggregated into rounded masses resembling lymph nodes. In places this inflammation has extended to tissues surrounding the joint laterally; about many of the blood vessels are rings of small mononuclear cells varying somewhat in width, with the walls of many infiltrated with the same kind of cells. There are also in one place a few hemorrhages 0.5 mm. in their largest diameters. The articular cartilages are necrotic or entirely absent, and the bone thus exposed is also necrotic near the surface. For a distance of 5–6 mm. from the edge of the joint, the articular cartilage on the head of the humerus is either entirely absent or represented by small, scattered, thin layers of granulation tissue (Fig. 7), which in places is very well organized resembling an old scar, and in other places less so. This granulation tissue, where it is well organized and at other points, is directly continuous with the loose and edematous tissue of the marrow cavities of the cancellous bone. It is about 0.5 mm. in depth at its thickest point. There are in the bone marrow spaces underlying the articular surfaces, numerous collections of mononuclear cells and many osteoblasts. This joint differs also from the other joints in the irregularities found on the surface of the humerus. The outer lateral surface of the humerus just below the head for a distance of 1 cm. has an irregularly scalloped

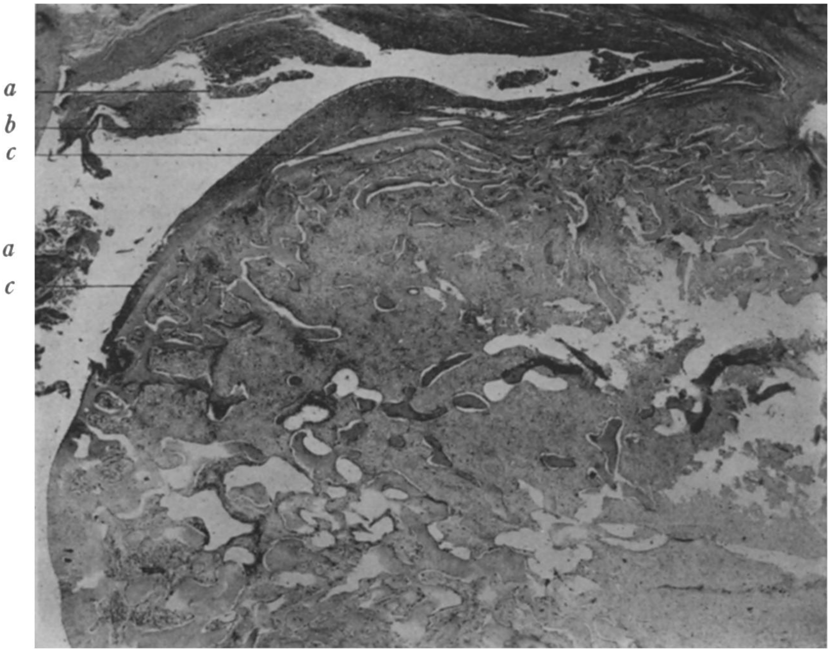

FIG. 7.—Part of the joint cavity from a rabbit killed two months and nine days after injection of streptococcus 256.

a. Exudate. *c*. Necrotic articular cartilage.
b. Granulation tissue which has grown over the articular cartilage.

appearance. These irregularities are elevated 1–1.5 mm. above the general level of the bone and constitute small but definite exostoses (Fig. 8). Around the outer edge, are large numbers of giant cells and internal to these are numerous small, newly formed marrow spaces and bone trabeculae. Still farther from the outer surface of the bone and near the newly formed bone are large numbers of osteoblasts.

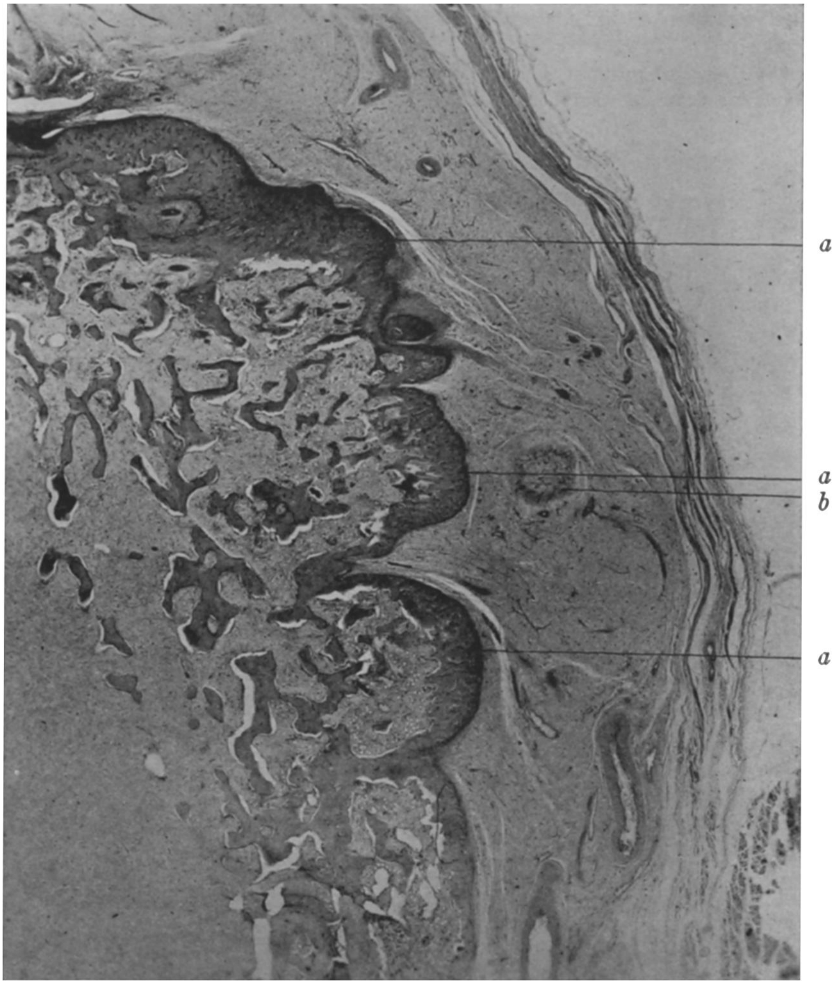

FIG. 8.—Outer lateral surface of the humerus near the head of the bone, from a rabbit killed two months and nine days after inoculation with streptococcus 256.

a. Exostoses. *b*. Nodule.

Changes in a rabbit killed 24 hours after intravenous injection of the 24-hour growth on blood agar slants of "Streptococcus viridans" obtained from the heart valves of a man who long had suffered with endocarditis. The same streptococcus was found during life in the tonsils. Other injections had been given over a period of three months at intervals of 4, 8, 7, 2, 14, 16, and 12 days each. The first two were of the 24-hour growth on one blood agar slant of "Streptococcus mucosus" (28) isolated from the middle ear. Each of the remaining injections were of the 24-hour growth on five blood agar slants of the "Streptococcus viridans" previously mentioned.—This rabbit received eight injections, the last one being given 24 hours before it was killed. The joint cavities contain a small amount o exudate consisting of a granular eosin stained material, polymorphonuclear leukocytes, and a few streptococci. This exudate is found in larger or smaller masses lying close against the synovial membrane. The cocci usually occur in pairs, sometimes in short chains. The capillaries along the edge of the joint cavities are filled with blood and occasionally organisms are found in them. There is an increase in the number of polymorphonuclear leukocytes present in the vessels and tissues surrounding the joints. At various points along the synovial membrane of some of the joint

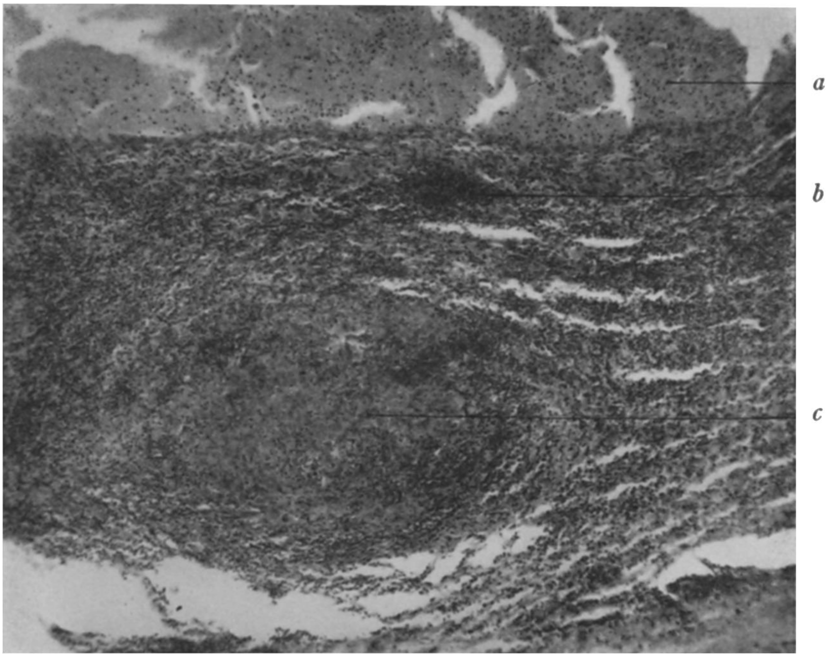

FIG. 9.—Exudate and tissue reaction with a nodule containing giant cells from the elbow joint of a rabbit killed four months after inoculation with streptococcus 34 from the Boston epidemic of sore throat (Dr. Fabyan).

a. Exudate in the joint cavity.
b. Collection of mononuclear cells.
c. Nodule composed largely of giant cells.

cavities and about small blood vessels in the plicae synovialis, there are collections of mononuclear cells with a few polymorphonuclear leukocytes. The mononuclear cells are chiefly of the smaller type. A considerable number of plasma cells are also present among them. In a few places the synovial fringes are necrotic. The surfaces of the articular cartilages are roughened and there are small regions of necrosis, some of them 0.5 mm. in length and often extending through the cartilage. In the diaphysis of the radius at a distance from the epiphyseal cartilage varying from 1.5 on one side to 0.75 mm. on the other is a region about 2 mm. wide in most places but extending about 1 cm. in a proximal direction along one side, in which osteoid tissue is abundant and osteoblasts numerous with only small patches of bone present here and there. This doubtless represents a healing infarct.

Changes in a rabbit killed four months after a single intravenous injection of the 24-hour growth on three blood agar slants of a streptococcus (34) obtained from Dr. Fabyan of Boston.—Sections of the left elbow and right tarsal joints were examined. In sections of the elbow joint the lateral portions of the cavity and the boundaries have the appearance of an abscess cavity and wall. The cavity contains blood with more than the ordinary number of large mononuclear cells. About the cavity is a well defined wall of cellular infiltration (Fig. 9) varying in width from 0.5–1 mm. with the synovial membrane absent except in a few places. The cells composing the wall are small deeply stained mononuclear cells, large endothelioid cells, large, very lightly stained cells with small vesicular nuclei, and multinucleated giant cells. The small mononuclear cells are most numerous and about half of them are plasma cells which are scattered more or less uniformly through the infiltrated region; the other small cells, although present in all parts of this region, have a tendency to arrange themselves about blood vessels and in groups of varying size. The large endothelioid cells are unevenly distributed and many of them contain pigment. In some places they are particularly abundant about the border of the cavity; in other places they occur in patches, some containing three or four, others 50 or more cells. The pigment-containing cells (Fig. 10) are most numerous in the parts more distant from the

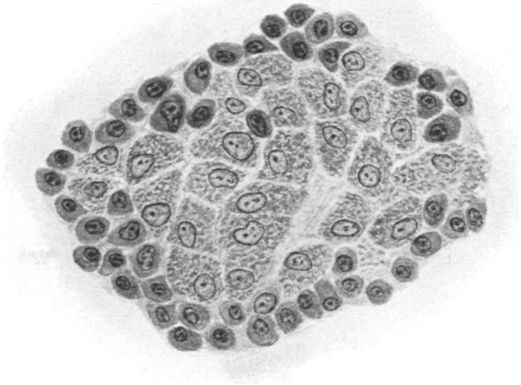

FIG. 10.—A group of large pigment-containing cells in the region of infiltration surrounding the elbow joint of a rabbit killed four months after injection of streptococcus 34.

margin of the cavity. The large, very lightly-stained cells occur in groups near the outer edge of the lesion and especially in those parts which approach nearest the external surface of the leg. Groups of these cells are also present in the tissues between the infiltrated zone and the surface. The giant cells (Fig. 11) contain 2 to 10 or 12 nuclei which are usually arranged about a central portion which contains red corpuscles, pigment, or a granular, pink-stained substance. They are arranged in groups, sometimes forming distinct nodules which are located near the margin of the cavity or at the outer part of the wall. The bone, except for a narrow strip bordering on the cavity which is necrotic, and the bone marrow, appear unchanged.

The contents of the left tarsal joint appear normal. The plica synovialis seems to be unchanged, being made up largely of fat cells. The surfaces of the articular cartilages (Fig. 12) are very irregular, due to partial or entire erosion of the cartilage and to outgrowths of cartilage into the cavity. There are also rather large necrotic regions in the cartilages which include the underlying bone for a short distance. In many places the cartilage cells are arranged in a very irregular manner, deeply-stained cells occurring in clumps singly or in groups and separated by rather wide spaces of cartilage containing no cells. In one place where the cartilage has been eroded for its entire depth, the space is filled in with a very vascular connective tissue which spreads out over the surface of the surrounding cartilage for a distance of 0.5 mm. There are collections of deeply staining mononuclear cells in many of the bone marrow spaces beneath the articular cartilages which have been injured. In one of the tarsal bones there are three small regions closely associated and somewhat rounded in shape with centers occupied by a lightly hematoxylin stained, finely granular substance in which are a few nuclei. About these regions is fibrous tissue arranged in a concentric manner.

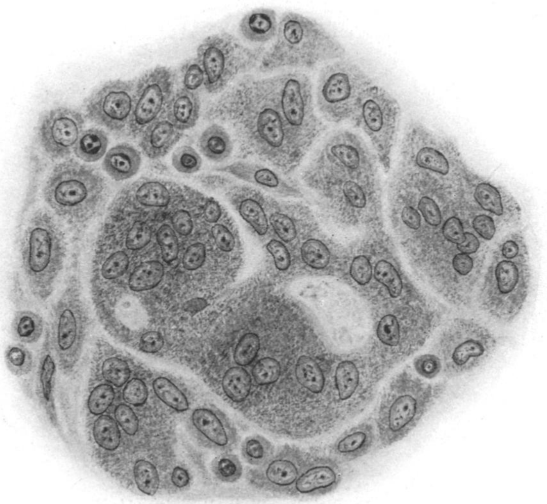

FIG. 11.—A nodule of multinucleated giant cells in the infiltrated region surrounding the elbow joint of a rabbit killed four months after injection of streptococcus.

Changes in a rabbit killed four months after a single intravenous injection of the 24-hour growth on two blood agar slants of a "Streptococcus viridans" (248) isolated from the crypts of the tonsils in a case presenting no evidences of endocarditis or arthritis.— Microscopic preparations of the left carpal and one tarsal joint were examined. The lesions found in the tarsal joint are fewer but of the same character as those found in the carpal joint. The synovial membrane and plicae synovialis appear unchanged. The fibro-cartilaginous portion and to some extent the adjoining articular cartilage are partially necrotic and in places have a shredded or coarsely fringed appearance with groups of cells arranged at intervals along the shreds or fringes. The surfaces of the articular cartilages are rather uneven, and there are small regions of necrosis, some extending nearly through the cartilage and a few shallow erosions. In places the cartilage cells are small and irregularly arranged. No lesions of the bone or bone marrow were observed.

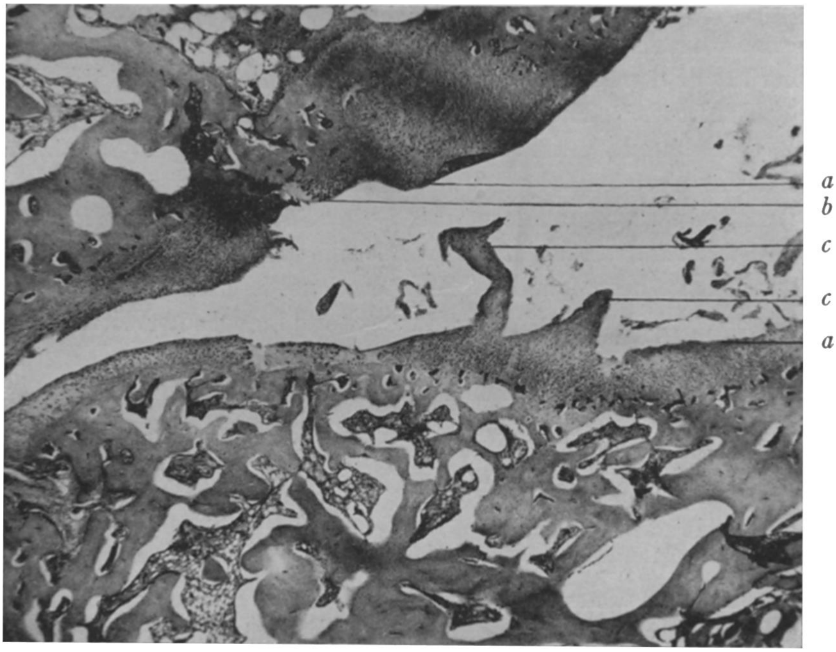

FIG. 12.—Ecchondroses of the cartilages of the tarsal joint of a rabbit killed four months after injection of streptococcus 34.

a. Articular cartilages.
b. Erosion of the cartilage.
c. Ecchondroses.

The differences in the inflammatory process in the joints of the 17 rabbits of this series studied at periods varying from two hours to four months (136 days) are only such as are consistent with the varying phases of a single inflammatory process, nor are there any striking differences in the reaction produced by the various kinds of streptococci employed. The changes in the joints of rabbits inoculated with hemolytic streptococci were studied after periods of 4, 5, and 70 days; those produced by *Streptococcus mucosus* at the end of 95 days, and the joint changes caused by *Streptococcus viridans* at the end of 136 days. The largest number of joints studied were from rabbits inoculated with streptococci isolated from human lesions produced by the milk epidemic and the peculiarities of these streptococci on culture media have been described by Dr. Davis.[1] These animals died or were killed after periods of 2, 4, 10, and 24 hours and 2, 3, 4, 7, 11, and 13 days. It may be that had more joints been studied from rabbits inoculated with the forms of streptococci least used, e.g., *Streptococcus viridans* and *Streptococcus mucosus*, some variation in the inflammatory process would have been found. The alterations described depend upon the early and apparently simultaneous and independent localization of the bacteria in the joint cavity, in the tissues surrounding the blood vessels of the synovial membrane, plica synovialis, tendon sheaths and blood vessels of the periosteum and bone marrow near the epiphyseal cartilages. The rather extensive involvement of the peri- and parasynovial structures such as tendon sheaths, epiphyseal cartilages and bone marrow is perhaps more marked than has been described by the authors quoted in the literature reviewed. The nodular formations developing in the tissues about the joints are essentially similar to those described in the myocardium of some of these same animals[2] and constitute a feature of the healing or later stages of the inflammation produced not only by *Streptococcus viridans* but also by the streptococcus from the epidemic.

Of two points deserving special mention, one is the vulnerability of the triangular, loosely constructed fibro-areolar tissue projecting into the joint laterally, the so-called plica which contains varying amounts of adipose tissue. It may be that the spirally arranged blood vessels here[3] offer exceptional opportunities for the lodgment of bacteria or are as much end vessles as those next to the epiphyseal cartilages. The other point concerns the influence on the character of the inflammatory process exerted by the peculiarities of joints in that they are at the same time free surfaces and closed cavities. Undoubtedly these features contribute in ways we do not fully understand to the results of infection, especially the absorption of inflammatory exudates and the extent to which healing is possible.

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[1] *Jour. Am. Med. Assn.*, 1912, 58, p. 1852.

[2] *Jour. Infect. Dis.*, 1912, 11, p. 243.

[3] L. Testut, *Traite d'anatomie humaine*, 6th ed., Paris, 1911, 1, p. 429.